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DIET AND CANINE HYSTERIA

EXPERIMENTAL PRODUCTION BY TREATED FLOUR*

BY

Sir EDWARD MELLANBY, K.C.B., M.D., F.R.S.

(From the Nutrition Building, National Institute for Medical Research, Mill Hill)

During the past twenty years or more dog-owners in this country and in the U.S.A. have been troubled by sporadic outbreaks of a nervous disorder which has been called canine hysteria, running fits, or fright disease. The condition seems to have been noted first in the southern States of the U.S.A. about 1916 and in England about 1924, and to have increased in intensity and distribution since then. Much has been written on the subject, and the disorder has at one time or another been ascribed to many causes. These include internal and external parasites ; deficiency of certain food factors, especially vitamins B_1 and A ; deficiency of an amino-acid such as lysine ; excess of proteins ; allergy to food constituents and other substances such as pollen ; toxicity of flour from the Far East ; yeast ; meat and the method of cooking it ; botulism ; infection of a virus type or a complication of distemper ; and, finally, heredity. In recent years, however, the majority of writers seem to have agreed that (1) food is the causal agent, though there is no agreement as to whether the trouble is due to a deficiency in the food or to a toxic agent ; (2) dog-biscuits and proprietary foods are often implicated ; (3) a wheat product is the most likely causal agent in the dog food, including the biscuits ; and (4) excitement and physical strain influence the onset and frequency of the attacks.

Canine hysteria up to 1936 has been reviewed and discussed by Hewetson (1936) ; here, therefore, reference will be confined to some of the experimental investigations on the subject since that date. Melnick and Cowgill (1937) produced convulsive reactions in six adult dogs on diets in which gliadin was the sole protein and furnished 16% or more of the calorie intake. They also suggested that the toxicity of these high-gliadin diets

* Preliminary report.

might be due to protein sensitization. Arnold and Elvehjem (1939) found that a dog food made of wheat flour and meat scrap processed by dry heat caused fits in young dogs, which could be alleviated or prevented by adding to the ration a sufficient amount of unheated protein or protein-containing foodstuff. They thought that a lysine deficiency was involved. Later, however, the subject was again investigated by Wagner and Elvehjem (1944) in consequence of an unpublished observation by Parry that commercial wheat gluten produced symptoms of hysteria in dogs with great rapidity and intensity. They confirmed Parry's observation and suggested that the disease was caused by some toxic factor in the wheat products and not, as the 1939 work had suggested, by a deficiency of lysine. Further, they stated that the attacks were not prevented by vitamin A, vitamin B_1, hydrochloric acid, casein, or casein hydrolysate.

Canine Hysteria as Observed in this Laboratory

Although there is general agreement among writers as to the signs of the disease and the behaviour of the affected animals, it is possible that canine hysteria has been occasionally mistaken for and even superimposed on such conditions as vitamin A or vitamin B complex deficiency. It may be said at once that in the work to be described no such complication could occur, since the animals always received ample amounts of yeast and vitamin A, except in a few experiments devised to test the effect of vitamin A deficiency on canine hysteria.

The actual observed state of the affected animals in the course of the work will now be given. Apart from the periods of the so-called "attacks," dogs subject to hysteria can usually be recognized by their general demeanour. As compared with normal dogs of the same litter, they tend (1) to be less interested in their surroundings; (2) to run or walk more slowly; (3) to lift their forelegs high when walking and to bounce along when running; (4) to have dry mouths; (5) to stand in a shady corner if the sun is shining and to resist persuasion to run about; and (6) to be less friendly and more frightened. Although the most severe attacks may develop suddenly, the above abnormalities are usually seen for some days before the onset of hysterical outbursts; the actual attacks seem to represent temporary exacerbations superimposed on a chronic abnormal condition.

Once having had fits, a dog will usually continue to suffer intermittent attacks until the diet is changed. The attacks may recur at intervals of several days or a number of fits of varying intensity may develop in one day; they tend to be induced by any sudden stimulus, nervous strain, or change of environment; even bringing susceptible dogs from an outside run to an indoor kennel often precipitates the attacks, as does moving the animals from their usual room to a warmer one. Lactating bitches appear to be particularly prone to hysterical fits.

If the harmful diet is continued for some months the fits may be reduced in number or even stop, but the animal's general behaviour remains abnormal, as described above. A time may come, however, when a dog which seems to be acquiring immunity suddenly suffers the most severe epileptiform fits and dies.

Attacks vary from what is called slight hysteria to true epileptiform fits. In *slight hysteria* the animal has a frightened look, and usually stands with either fore or hind legs rather apart and ears back. Jerking of the head backwards may be seen. At this stage the animal will sometimes shake itself, take a drink of water, and then recover. Often the attacks begin as above, after which the dog rushes across the cage or run, but after dashing into the wall sits down, quiet and dejected-looking, and then slowly recovers. This is recorded as *hysteria*. In more severe cases the animal sits in a sphinx-like posture; its head soon starts jerking, and the movement spreads throughout the body. Next it starts running round and round its cage, sometimes barking furiously, and either dashes into the walls, apparently without seeing them, or attempts to jump up them, overturning food dishes and water-pots, and getting both itself and its cage into a filthy condition. It may begin to recover at this stage, stop running, and stagger round like a drunken person. It will sit down, looking very miserable, but at the end of about 30 minutes may be more or less normal. This is recorded as a *hysterical fit*.

If the dog does not recover at this stage it goes on running, froths at the mouth, usually howls, and collapses. Even then it still moves its legs with a running movement. Finally this movement ceases and the animal remains still, with rather deep breathing. After a varied time—5 to 30 minutes—which appears to bear a relation to the severity of the fit, it recovers consciousness, gets up, and staggers around with marked ataxia; then follow the recovery stages outlined for a hysterical fit. This is recorded as a true *epileptiform fit*. If the animal does not recover consciousness within about thirty minutes it usually dies, although it may remain in an unconscious state for anything up to 36 hours.

Basis of Present Investigation

By 1931 the idea had developed in this laboratory that outbreaks of hysteria were due to the bread portion of the diet, and, since that time, when any such outbreak has occurred the source of the bread supply has often been changed and the fits have usually ceased. Another method adopted empirically, and because we had never seen a dog develop this hysterical condition when oatmeal formed the major part of the diet, was to replace a half or more of the bread by oatmeal, and this was also effective in stopping the outbreak. Samples of the flour from which the suspected breads had been made were obtained for inspection, and thanks are due to a number of bakeries for help in this connexion.

During the period of the war it became necessary to obta supplies of flour of known extraction and composition f experiments on nutrition, and the Cereal Division of t Ministry of Food arranged that these supplies should be pr pared at one mill. The miller responsible for the productic of the flour often kindly brought it in person to the laborator and it was natural to tell him that we suspected some flou of being responsible for outbreaks of canine hysteria a thought a bleaching or improving process might be doing t harm. He asked to be shown samples of the flours, a immediately on seeing them said that all had been heavi bleached and probably improved.

The following are the chemical agents in use for bleachi and improving flour (Lockwood, 1945 ; Smith, 1944):

Bleachers.—Nitrogen peroxide (gas); benzoyl peroxide (powde

Improvers.—Ammonium persulphate (powder); potassium p sulphate (powder); potassium bromate (powder); acid calciu phosphate (powder).

Combined Bleachers and Improvers.—Chlorine (gas); chlorine a nitrosyl chloride (beta gas); nitrogen trichloride (agene) (gas chlorine dioxide (addage) (gas).

Thus there seemed a large choice from which to pick out t hypothetical offending agent. However, in discussing t matter further with the miller, the possible implication of whe protein as the aetiological factor in canine hysteria was me tioned, reference being made to the results obtained by Melni and Cowgill on gliadin and by Wagner and Elvehjem on whe gluten respectively. Thereupon he said it was well known th the agene process, in which NCl_3 gas was used, affected t gluten of flour, and that this method of improving flour w used very extensively. On being challenged on this point, said he would not be surprised if as much as 90% of flo milled in this country and used for bread-making w "agenized." He was therefore asked to supply this laboratc with agenized flour and an equal amount of untreated flo from the same grist so that the hypothesis could be experime tally tested. These are the flours described in this paper treated (agenized) and untreated (no agene).

Agene is said to consist of approximately 1% nitrogen t chloride in air saturated with water-vapour. The gas generated by bringing together chlorine, water, and ammoni chloride, and is removed from the solution by aeration ; t air and gas are then brought into intimate contact with the flo in an agitator. The amount of agene used in any operati can be closely controlled and depends largely on the extracti rate of the flour or on the particular portion of the wheat be milled.

Experimental Results

The flours were tested by feeding young dogs of the sa litter on treated and untreated samples. The diet used was c known to be adequate and compatible with normal growth a

health provided untreated flour or oatmeal was used as the cereal. It consisted of: separated milk powder, 20 g.; cereal, 50–340 g.; lean meat, 15 g.; peanut oil, 10 ml.; bakers' yeast, 5% of the cereal; ascorbic acid, 5 mg.; NaCl, 1–2 g.; vitamin A, 2,000 or 3,000 i.u.; and vitamin D_2, 200 i.u. The cereal of the diet was cooked in a steamer for 90 minutes at a pressure of 0.5 lb.

It soon became evident that the hysterical outbreaks could often be produced by the above diet if it contained the treated flour but not if it contained the untreated flour. In young puppies the attacks came on insidiously and usually took some weeks to develop. In older growing animals, whose appetites were larger, it was often possible to produce the condition more quickly—sometimes after a fortnight or less of feeding on a diet which included agenized flour. The degree of susceptibility varied from litter to litter and even from animal to animal in the same litter. Changing the flour in the diet of a badly affected animal to the untreated variety resulted in a sudden stoppage of the fits, but the animal might remain nervous and shy for a period.

Tables I–III show the effect of the treated (agenized) as against the untreated flour in regard to the number of hysterical attacks and fits produced in the animals. Attacks of slight hysteria have not been tabulated, but these were numerous in the animals receiving treated flour and were never seen in those having untreated flour. All the attacks recorded were observed, except those in the column headed "probable fits," which were deduced from the condition of the animal and its cage after periods when observation was not continuous. Many of these so-called "probable" fits were without doubt severe hysterical fits, for both animals and cages were filthy, water-pots and food dishes were overturned, and sawdust scattered, as was the case after observed fits. The cages of the animals receiving treated flour were often found in this condition in the early morning, suggesting that the night may be a common time for the attacks; but, since the severity of an attack could not be judged solely from the state of the cage after a lapse of possibly several hours, these hypothetical fits have not been included in the tables.

TABLE I

Dog No.	Type of Flour	Time to First Attack	Hysteria	Hysterical Fits	Epileptiform Fits	Probable Fits	Total
			1st Period (24 *weeks*)				
3175	Untreated	—	0	0	0	0	0
3176*	Treated	4 weeks	0	10	5	5	20
3177	,,	4 ,,	9	10	6	5	30
			2nd Period (12 *weeks*)—*Flour reversed*				
3175	Treated	1 week	15	6	1	2	24
3177	Untreated	—	0	0	0	0	0

* Died after 6 weeks on diet, after having continuous epileptiform fits for two days.

It is seen from Table I that during the first period of 24 week dog 3175, receiving untreated flour, had no hysteria or fits, whil 3177, which received the treated flour, had 30 attacks of variou kinds. During the second period, lasting 12 weeks, when th types of flour were reversed, dog 3175 suffered from 24 attack and 3177 had none.

TABLE II

Dog No.	Type of Flour	Time to First Attack	Hysteria	Hysterical Fits	Epileptiform Fits	Probable Fits	Tota
3187*	Treated	4 weeks	5	7	3	1	16
3188	,,	4 ,,	4	9	0	4	17
3189	Untreated	—	0	0	0	0	0
3190†	Treated	4 weeks	4	13	6	4	27
3191	,,	4 ,,	5	11	2	3	21
3192	Untreated (1st 15 weeks)	—	0	0	0	0	0
	Treated (8 weeks)	2 weeks	2	2	0	1	5

* Died after 23 weeks on diet after having a severe epileptiform fit.
† Died after 15 weeks on diet after having continuous epileptiform fits f 36 hours.

Table II also shows how definite is the effect of the agenize flour. The one dog of the litter having the untreated cere throughout, No. 3189, had no hysterical bouts or fits during th experimental period of 22 weeks, whereas the four havir treated flour all the time had attacks varying in severity ar ranging in number from 16 to 27 during this period. The la of the series, No. 3192, whose diet was changed in the course the experiment, had no fits during the 15 weeks it received u treated flour, but two weeks after the substitution of treate (agenized) flour the attacks started, and it had five of them.

Vitamin A Deficiency and Canine Hysteria

Canine hysteria can be superimposed on vitamin A deficien when animals have a diet deficient in vitamin A and containi agenized flour. Examples are seen in Table III, which sho the results of an experiment made on four dogs of the sa litter, two of which had the basal diet described above, co taining 2,000 i.u. of vitamin A daily, and the other two had t same diet with the omission of the vitamin. No hysteria fits developed in any of the dogs during the 15 weeks wh untreated flour was given, whether vitamin A was included the diet or not. In the second period treated (agenized) flo was substituted for the untreated type in each case, and a four animals suffered to some extent from hysteria or fi though the vitamin A content of the diet remained the sa as during the first period. After 10 days on this diet untreat flour was again given to two of the animals—Nos. 3203 a 3205—the first being vitamin-A-deficient and the other norm The flour has now been changed for one month, but, exce during the first day, neither dog has had any form of fit, a

hough not yet fully recovered, they have had no outburst which ould be rated even as slight hysteria.

TABLE III

Dog No.	Vitamin A in Diet	Type of Flour	General Condition of Animal	Hysteria and Fits
		1st period (15 *weeks*)		
3201	−A	Untreated	Definite A deficiency	None
3202	+A	,,	Normal	,,
3203	−A	,,	Definite A deficiency	,,
3205	+A	,,	Normal	,,
		2nd period (10 *days*)		
3201	−A	Treated	Definite A deficiency	Slight hysteria
3202	+A	,,	Normal	4 hysterical fits
3203	−A	,,	Definite A deficiency	8 severe epileptiform fits
3205	+A	,,	Normal	4 ,, ,,

Discussion

The results of this investigation show that the practice of leaching and improving flour by NCl_3, known as the agene rocess, is responsible for a flour which produces canine ysteria under the conditions described above. The evidence of a direct kind, the abnormality being produced by diets ontaining the treated flour, samples of the same flour ntreated being harmless. Substitution of the treated flour y the untreated type tends to reverse the animal's condi- on and allows complete recovery from the hysteria and fits, ven though the animal itself may not be normal. Recovery om the slighter but more chronic condition appears to bear a elationship to the length of time the animals have received e treated flour. If they have had it for a long period— g., six months—recovery may not be complete even after ree to four months on the untreated flour, although the more vere abnormalities, such as hysterical and epileptiform fits, ill cease within 24 to 48 hours of the change of diet.

In this connexion the Report of the Departmental Com- ittee on the Treatment of Flour with Chemical Substances 927) states: " An obvious method of investigating the presence harmful compounds or suspected impairment of nutritive operties is by feeding experiments with animals. When such periments give positive results they are conclusive, but nega- e results cannot be regarded as innocuous." The results scribed in this paper are of the positive kind referred to in is statement. It is, however, of interest to note that during e course of the present work feeding experiments on rats th agenized flour were negative, just as similar experiments ferred to in the report of the Departmental Committee on eding rats with flour treated commercially with chlorine and trogen trichloride were " inconclusive."

It is agreed by experts in milling practice that the agene pro- ss affects the gluten of flour particularly. In the above- entioned report it is stated that " chlorine can act energetically

upon gluten, and that the nature of the reaction includes t entrance of chlorine into such important parts of the glut complex as the tyrosin and tryptophane groupings"; an later, that "our observations upon chlorine apply also nitrogen trichloride" and "evidence has been given that action [i.e., that of NCl_3] on the protein of flour is probab similar to what we have already described in the case chlorine." No experiments have been made in the prese work with flour bleached and improved by chlorine.

These statements from the report, written nearly 20 yea ago, taken in conjunction with the results obtained in t present work showing the toxic effect of agenized flour, mu be considered in relation to the work of Melnick and Cowg (1937), of Parry, and of Wagner and Elvehjem (1944), referr to earlier, and it would be a matter of interest to know wheth the gliadin and gluten used by the U.S.A. workers were p pared from agenized flour. It is believed that this process improving flour is, or has been, as popular in the U.S.A. in this country, so it is not unlikely that the proteins used the U.S.A. workers were prepared from agenized or simila treated flours. Obviously the next test to be made in rega to canine hysteria was to compare the effects of wheat glut made from untreated and agenized flour respectively, and t is now being done.

When the idea of testing the effect of agenized as agai untreated flour was first mooted the point was raised th though proprietary dog-biscuits were said to be associated w canine hysteria, it seemed unlikely that the flour used in su biscuits would be agenized. The miller, however, said th although flour intended solely for dog-biscuits would usually be subjected to an improving process, a long-extract flour which had been so treated was, in fact, often used in th manufacture. Indeed, he regarded this fact as supporting idea that agenizing might well hold the solution to the probl of the observed hysterical attacks and account for the variati in reports implicating dog-biscuits.

The agenized flours used in this investigation were specially prepared overbleached specimens, but, according our miller friend, were all subjected to a normal commer bleach. At different times the extraction rate of the flours varied between 80 and 90%. Some batches have had no ad calcium and others have had the normal statutory additi prescribed for 85 and 90% extraction flours, but all, irresp tive of calcium content or extraction rate, have given the sa results so far as canine hysteria is concerned. It is poss to increase the bleach in order to camouflage a clumsy sepa tion in the mill. It is likely that such a flour would be e more powerful in producing the hysterical condition h described.

The abnormal behaviour of the animals affected by agenized flour suggests that the central nervous system

primarily affected by some toxic agent, but other organs may also be involved. A few dogs have died in these attacks, but ordinary post-mortem examination has not yet revealed any lesion which can be regarded as the essential one. It is clear that investigations must now be made to see whether human beings are affected by bread made from flour improved by NCl_3.

Summary

Canine hysteria, sometimes called running fits or fright disease, a nervous condition which has troubled dog-owners both in this country and in the U.S.A. for the past 20 years or so, has been produced in growing dogs by including in their diet flour that has been improved and bleached by NCl_3, the agene process. The same flour when untreated did not produce the nervous malady. Affected dogs returned towards normal and the typical hysteria and fits stopped when the agenized flour was removed from the diet and replaced by unimproved flour of the same grist.

Warm thanks are due to the miller mentioned above, who wishes to remain anonymous, for the help he has given in this work. Not only did he supply with promptness and great care the specimens of flour needed for the research, but he also placed his specialist knowledge as a scientific miller at our disposal and so made the investigation possible. I wish also to thank members of the staff of the laboratory, especially Mr. R. J. C. Stewart, for their help and zeal in this work.

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